(a) a nucleic acid segment comprising a sequence region that consists of at least 14 contiguous nucleotides that have the same sequence as, or are complementary to, 14 contiguous sequence nucleotides of SEQ ID NO:1; or

(b) a nucleic acid segment of from about 14 to about 10,000 nucleotides in length that hybridizes to the nucleic acid segment of SEQ ID NO:1 or the complement thereof, under hybridization conditions of high stringency including a temperature of about 50°C to about 70°C and a salt concentration of about 0.02 -0.15 molar NaCl.

REMARKS

Status of the Claims:

Claims 1 and 7 have been amended. Claims 36 and 38 have been canceled. Claims 1, 7, 8, 10-25, 34-35 and 37 are pending in the case.

Rejection of Claims 7, 34-36 and 38 Under 35 U.S.C. §112, Second Paragraph:

Claims 7, 34-36 and 38 have been rejected under 35 U.S.C. §112, second paragraph for failing to particularly point out and distinctly claim the subject matter regarded as the invention.

The action has objected to lack of specificity in the term "high stringency" in claim 7. Applicant has amended claim 7 to particularly specify that conditions of high stringency include a temperature of about 50°C to about 70°C and a salt concentration of about 0.02-0.15 molar NaCL. The meaning of "high stringency" is clearly defined in the specification, particularly on

page 35 beginning at line 16-24 and the references found in lines 25-28, the text of which is incorporated by reference.

Claims 36 and 38 have been canceled; therefore, the lack of meaning of "T98G" as unclear is no longer an issue.

Rejection of Claims 34 and 35 Under 35 U.S.C. §112, Fourth Paragraph:

Claims 34 and 35 have been rejected under 35 U.S.C. §112, fourth paragraph for failing to further limit claim 1. It is the examiner's position that these claims depend on a claim and merely recite proper use inherent to the DNA segment of claim 1. The action further argues that these claims are misleading because they imply MTAP has tumor suppressor properties. The action opines that it is "probably" other genes such as P16 also known as MTS1 that have tumor suppressor function which would be present in the DNA segment comprising SEQ ID NO:1. Applicant's amendment to claim 1 more clearly indicates that the referenced DNA segment is the MTAP gene and does not include other genes.

Rejection of Claims 1, 7, 8, 10-12, 15, 17, 18, 20, 21, 34 and 35 under 35 U.S.C. §102(b):

Claims 1, 7, 8, 10-12, 15, 17, 18, 20, 21, 34 and 35 have been rejected under 35 U.S.C. §102(b) as anticipated by Kamb, *et al.* (1994). The action asserts that Kamb, *et al.* disclose tumor suppressor gene MTS1 which maps to 9p 21-22. The action further states that the cosmid containing MTS1 also contains MTAP because the two genes are tightly linked. The action

concludes that the DNA segment in the cosmid comprises SEQ ID NO:1 and therefore the MTAP gene.

Applicant believes that the action has improperly ascribed information to the Kamb, *et al.* reference that is not disclosed. The cited reference describes work aimed at searching for candidate tumor suppressor genes. During this search the DNA sequence parts of cosmid C5 were sequenced and identified as the MTS1 and MTS2 genes. The publication reports DNA sequences for the two closely related genes MTS1 and MTS2 but does not identify, isolate or sequence the MTAP gene of the present invention. As is well established by the courts, conception of a gene does not occur until the gene is defined so as to distinguish it from other materials as well as how to make it (see Amgen, Inc. v. Shugai Pharmaceuticals Company, Ltd., 927 F2d 1200 (Fed. Cir. 1991). Kamb, *et al.* do not disclose MTAP gene nor do they disclose its DNA sequence.

Rejection of Claims 1-12, 15-18, 20-25 and 34-38 under 35 U.S.C. §102(b):

Claims 1-12, 15-18, 20-25 and 34-38 have been rejected under 35 U.S.C. §102(b) as anticipated by the Bohlander, *et al.* (1994) reference. The action refers to the Bohlander, *et al.* reference as disclosing a chromosome fragment comprising the MTAP gene, kits and methods of use indicating that, as shown in FIG 4 of the reference, chromosome segments comprising the MTAP gene inherently comprise SEQ ID NO:1.

Applicant respectfully points out that this paper in no way discloses the MTAP gene. Attention is directed to the bottom of page 215 where the authors indicate that there might be

tumor suppressor genes other than MTS1 and MTS2 located in the region centromeric to the IFN gene cluster. The paper does not disclose the MTAP gene. The paper describes several DNA probes. Such probes are based on DNA fragments from a microdissected chromosomal fragment taken from 15 chromosomes in the region 9p21-23. At most, the paper reveals that some of the single copy clones originated from the 9p21-23 area of the chromosome might be useful as probes for this region of the chromosome. Reported results indicate generation of a long-range genomic map and the localization of CDKN2 gene which in combination with an unidentified closely related gene was indicated to include the MTS1 and MTS2 genes reported by Kamb, *et al.* Applicant therefore respectfully suggests that the Bohlander, *et al.* paper merely describes probes that may ultimately lead to the identification, isolation and characterization of novel tumor suppressor genes in the 9p21 region.

Rejection of Claims 1-12, 15-18, 20-25 and 34-38 under 35 U.S.C. §102(b):

Claims 1-12, 15-18, 20-25 AND 34-38 have been rejected under 35 U.S.C. §102(b) as anticipated by the Nobori, *et al.* (Nature 1994) reference. The action takes the position that the Nobori, *et al.* report discloses MTAP cDNA, its gene and a specific portion or region of the gene designated T98G as well as kits and methods of use.

The Nobori, *et al.* publication reports the sequence analysis of the CDK41 coding region of a lymphoblastoid cell line and speculates that the CDK4 inhibitor is a strong candidate for a melanoma susceptibility gene. A 19-kb λ-phage clone designated 10B1 was subcloned and the CDK4 inhibitor identified. CDK4 was said to contain an open base reading frame with a

sequence identical to a previously reported CDK4 inhibitor. The reference showed a physical map of chromosome 9p21 between two gene loci (*i.e.* MTAP and IFN-β). One should note that the enzyme encoded by the MTAP gene was known and that the general location of the MTAP gene on the 9p21 chromosome was also known. However, characterization, isolation and sequencing of MTAP was not disclosed and probes from the 3' end of the MTAP gene were, in fact, employed to study absence or rearrangement of the CDK4 inhibitor gene in malignant cell lines, not to isolate, sequence and characterize the MTAP gene..

Applicant concludes that Nobori, *et al* do not disclose the MTAP gene because the MTAP gene had not been isolated and sequenced, nor is there mention of kits or methods of use for the MTAP gene.

Rejection of Claims 26 -33 Under 35 U.S.C. §102(b):

Claims 26-33 have been rejected under 35 U.S.C. §102(b) as anticipated by Nobori, *et al.* (Cancer Research, 1991) or Nobori, *et al.* (Cancer Research, 1993). The action states that the references disclose methods, kits and antibodies that bind to MTAP (protein) and that the MTAP (protein) is linked to alkaline phosphatase through a secondary antibody or linked to an label at protein A.

Applicant directs attention to the subject matter of the Nobori, *et al.* references, *i.e.* methylthioadenosine phosphorylase which is a polypeptide, not a gene. Having the peptide does not mean one is in possession of the gene, see *In re* Bell, where the court noted that knowing the structure of the protein does not render obvious the encoding gene (26 USPQ2d, 1529, 1531

(1993)). By logical extension, if not obvious, knowledge of the protein does not anticipate the gene.

Rejection of Claims 37-38 Under 35 U.S.C. §102(b):

Claims 37 and 38 have been rejected under 35 U.S.C. §102(b) as anticipated by Scaletti, *et al.* (1987). Scaletti, *et al.* is said to disclose methods of distinguishing tumor types by comparing chromosome 9p patterns between tumor types.

Applicant has studied the abstract by Scaletti, *et al.* and fails to find a description of distinguishing tumor types by comparing chromosome 9p patterns. The cell lines studied indicate normal chromosome 9 findings on all but two cell lines. Those two cell lines show a deletion and in one an additional inversion. In fact, the abstract notes that while the enzyme MTAP is deficient in acute leukemia cases it is apparently "not associated with a frequent cytogenetic abnormality of chromosome 9p". It appears to applicant, therefore, that Scaletti, *et al.* were not able to distinguish tumor types by comparing chromosome 9p patterns. This publication in no way anticipates the use of MTAP pattern of 9p homozygous deletions and associating the patterns with patterns obtained from the tumor to be identified.

Rejection of the Claims Under 35 U.S.C. §102(a):

The claims have been rejected under 35 U.S.C. §102(a) as anticipated by the Porterfield, *et al.* (1994), the Dreyling, *et al.* (Cancer Research, 1995) and the Olopade, *et al.* (PNAS, 1995) references. Applicants submit herewith a Declaration indicating that Dr. Olopade and not the

other authors mentioned on these papers was the sole inventor of the subject matter disclosed and claimed in the present application. It is respectfully submitted that with this declaration the §102(a) references are no longer citable as prior art.

Applicant submits that none of the references cited by the action as anticipatory of the subject matter disclosed and claimed in the present application is citable as anticipating the claimed subject matter. Applicant is the first to have isolated and sequenced the MTAP gene. The enzyme encoded by the gene had been previously known; however, only the general location of the MTAP gene was recognized. As noted by the court in Amgen, Inc. v. Shugai Pharmaceutical Company, Ltd., 927 Fed. 2d 1200 (Fed. Cir. 1991) "...conception has not been achieved until reduction to practice has occurred, *i.e.* until after the gene has been isolated." (*Id.* 1206). None of the references had identified the structure or physical characteristics of the MTAP gene. In fact, the publications containing any DNA sequences are focused on the CDK4 genes.

The action's position appears to be that because a large piece of DNA that may contain the MTAP gene but which has not been sequenced and from which the MTAP gene has not been isolated, anticipates the MTAP gene. This contradicts the position taken by the courts which have repeatedly emphasized that a gene is a chemical compound and that conception of chemical compounds require the definition of that compound (see Okaa, 849 F2d at 583, 7 U.S.P.Q. 2d at 1171, 1988). Conception is classically defined by the courts as "the formation in the mind of the inventor, of a definite and permanent idea of the complete and operative invention, as it is

hereafter to be applied in practice." (Hybridtech, 802 Fd at 1376, 231 U.S.P.Q. at 87, and citations therein).

Applicant's position therefore is that the MTAP gene is not disclosed in any of the cited references and is not sufficiently characterized in any way to indicate that the authors of the references had conception of the gene.

Applicant intends this to be a complete response to the examiner's action and reconsideration of the application is respectfully requested. Should any further issues remain, the undersigned attorney respectfully request a telephone call at 512-418-3108.

Respectfully submitted,

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